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## Re--direction of interferon gamma and its signaling moiety

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*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

2012

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Bansal, R. (2012). *Re--direction of interferon gamma and its signaling moiety: new options for the therapy of chronic diseases*. s.n.

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# Appendices

A grayscale microscopic image of tissue, showing various cellular structures and patterns, serving as a background for the list of appendices.

List of Abbreviations

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**List of Abbreviations:**

<b>ALT</b>	Aspartate aminotransferases
<b>AST</b>	Alanine aminotransferases
<b>Ang1</b>	Angiopoietin 1
<b><math>\alpha</math>-SMA</b>	Alpha-smooth muscle actin
<b>AUC<sub>0-∞</sub></b>	Area under the curve from zero to infinity
<b>BiPPB</b>	Bicyclic PDGF $\beta$ R-recognizing peptide
<b>CCl<sub>4</sub></b>	Carbon tetrachloride
<b>CD</b>	Cluster of differentiation
<b>CXCR4</b>	CXC Chemokine receptor 4
<b>DAPI</b>	4',6-diamidino-2-phenylindole
<b>DMF</b>	Dimethyl formamide
<b>ECM</b>	Extracellular matrix
<b>eNOS</b>	Endothelial nitric oxide synthase
<b>FCS</b>	Fetal calf serum
<b>FITC</b>	Fluorescein isothiocyanate
<b>GAPDH</b>	Glyceraldehyde 3-phosphate dehydrogenase
<b>GMBS</b>	N-[ $\gamma$ -maleimidobutyryloxy] succinimide ester
<b>HE</b>	Hematoxylin
<b>HSCs</b>	Hepatic stellate cells
<b>HSA</b>	Human serum albumin
<b>IDO-I</b>	Indoleaminepyrrole 2,3-dioxygenase-I
<b>IFN<math>\alpha</math></b>	Interferon alpha
<b>IFN<math>\beta</math></b>	Interferon beta
<b>IFN<math>\gamma</math></b>	Interferon gamma
<b>IFN<math>\gamma</math>R</b>	Interferon gamma Receptor
<b>Ig</b>	Immunoglobulin
<b>IL</b>	Interleukin
<b>Mal-PEG-SCM</b>	Maleimide-PEG-succinimidyl carboxy methyl ester
<b>MFs</b>	Myofibroblasts
<b>MHC-II</b>	Major histocompatibility complex-II
<b>MimIFN<math>\gamma</math></b>	Mimetic Interferon gamma

<b>MIP2</b>	Macrophage inflammatory protein 2
<b>MMPs</b>	Matrix metalloproteinases
<b>mPEG-SMB</b>	PEG-succinimidyl $\alpha$ -methylbutanoate
<b>NET</b>	Norepinephrine transporter
<b>NO</b>	Nitric oxide
<b>PAS</b>	Periodic acid schiff's base
<b>PBS</b>	Phosphate buffered saline
<b>PDGF</b>	Platelet derived growth factor
<b>PDGF<math>\beta</math>R</b>	Platelet derived growth factor beta receptor
<b>PEG</b>	Polyethylene glycol
<b>PPB</b>	PDGF $\beta$ R-recognizing cyclic peptide
<b>SATA</b>	N-succinimidyl-(acetylthio)-acetate
<b>SDF1<math>\alpha</math></b>	Stromal cell-derived factor 1 alpha
<b>STAT1<math>\alpha</math></b>	Signal transducer and activator of transcription 1 alpha
<b>Th</b>	T helper
<b>TIMPs</b>	Tissue Inhibitor of metalloproteinases
<b>TRITC</b>	Tetramethyl Rhodamine Isothiocyanate
<b>TNF<math>\alpha</math></b>	Tumor necrosis factor alpha
<b>VEGF</b>	Vascular endothelial growth factor

## Acknowledgements

Foremost, I wish to thank **god** for all His blessings, for giving me enough strength to believe in myself and to accomplish my dreams. I could never have done this without the faith I have in You, **the Almighty**.

My most sincere gratitude and appreciation are dedicated to my promoter, **Klaas Poelstra** for his guidance, mentorship, encouragement and support at all levels. These past years working with you were truly invaluable and rewarding experience for me. I appreciate your concerns, your kind attitude and motivation that kept me going further while overcoming the frustrations of unsuccessful experiments and paper rejections. I also would like to thank you for providing me enough support and opportunities to attend the national and international scientific meetings which really helped me think beyond my scientific research and gave me new horizons to pursue my career in research. Apart from research, I learnt a lot from you, which I am sure, will be useful in different stages of my life.

I am thankful to my co-promoter **Jai Prakash** for his immense supervision, criticisms and valuable comments. Jai, I must admit that I have learned so much from you. Your practical skills, profound knowledge and continuous help from designing experiments to analyzing the results helped me becoming independent at the later stage of my research. Our vigorous discussions on experiments, presentations and publications led me to think innovatively, to enhance my knowledge and to improve my presentation skills. I wish you very good luck for your future career and for your new ventures at Karolinska Institute.

I would like to extend my sincere thanks to **Leonie Belaars**, my co-promoter for her helpful comments, suggestions and discussions during my research. I had a great time with you in EASL, Vienna where we had discussions about research and life. I am thankful to you for providing me support and motivation to continue my path as a scientist.

I express my heartfelt gratitude to the doctoral reading committee members, **Prof. Detlef Schuppan**, **Prof. Han Moshage** and **Prof. Gert Storm** for reviewing my thesis and providing their valuable suggestions and comments.

I am grateful to acknowledge **Hans, Geny** and **Barbro** for their helpful comments and suggestions during the research meetings. **Hans**, thanks for guiding me through the pharmacokinetic data analysis. I want to thank **Geny** for her expert comments and critical remarks during my presentations, which certainly helped me to improve the quality of publications. I am also thankful to you for your concerns and your support during my stay in Groningen. **Barbro**, you joined the group 1 year before I left and we had few discussions about immunology but more discussions on life and science. Your knowledge and spirit in research always inspired me. I am also thankful to **Herman Steen** for his encouragement, for providing me opportunity to give presentations at BiOrion and above all for bringing my doctoral research further to translational phase through BiOrion.

I am short of words to thank **Jan Visser** and **Riet. Jan**, you helped me a lot in labs from opening tight bottles to finding every small thing. You always made me feel comfortable and always motivated me during my research. I am thankful to you and **Riet** for your care and warmth, which will always be treasured, in my remembrances. You both helped us in house shifting, at the time of Ishaan's birth and carried us when we needed an elderly advice. In Groningen, you are still like our family and we undoubtedly relied on and never hesitated to call you even in the middle of the night. We have spent so many unforgettable moments and really I would never forget you both throughout my life. **Riet**, I want to thank you for becoming my paranymp.

Special mention and thanks goes to **Eduard**. It took me a while to start working with you and to understand you. But when we started to work together, it was so much fun and your help in animal experiments during any time of the week and weekends were quite exceptional. I barely find words to thank you enough for your help at the later stages of our stay in Groningen. I am very happy that you are my paranymp and I hope we will stay in touch always.

Words of thanks are due to **Catharina** for her continuous assistance, support and the protocols. I express my thanks to **Alie** and **Marieke** for their help at the later stage of my doctoral thesis because of which I could manage to finish experiments in time. I also want to thank you all for being good friends and for your immense care.

I am grateful to **Gillian** for her assistance in the official work, in filling dutch forms, arranging letters and especially helping me at the final stages of thesis after moving to Sweden. I also thank you for being a good friend, for fun-loving and caring talks.

I am thankful to my colleagues at the department of Pharmacokinetics, Toxicology and Targeting for your care and support. I had great fun with **Adriana, Marianna, Marlies, Marike, Rose, Martin** and **Venkatesh**. I enjoyed the get-togethers, dinners, labdays and cake treats. Gestures of thanks are due to **Marike, Marlies, Adriana** and **Marianne** for being great friends and colleagues, for your continuous support and for the dinners we had together. **Marike**, I want to thank you for being a great company at conferences at Keystone and Boston, for helping us moving and also for visiting us in Stockholm. I am also thankful to Peter, Magdalena, Na, Xiayu, Mackenzie, Inge De Graaf, Inge Weestra, Marieke, Marjolijn, Marina, Paul, Mieke, Christina, Carian and students at the department for their cooperation rendered during my stay.

I cherish the friendship I had and take this opportunity to thank each one of them. To **Vinay-Chetna, Anil, Vaishali-Pranav, Tushar, Avinash-Shilpa, Prashant-Aradhana, Ratna-Kalyani, Raj-Shirisha, Ranjeet-Kavita, Pandey ji-Shweta** and **Dhar Uncle-Aunti** for their constant support and whole hearted solidarity. I especially want to thank **Pandey ji** and **Shweta** for providing us place to stay in your house before moving to Sweden. I also thank Groningen Indian Student Association (**GISA**) for organizing cultural and interactive programs on several occasions that made me to realize the scent of Indian festivals being away from home. I want to especially thank **Dipika**, my best friend and my little sis who always stayed with me at my good times and bad times. Her love and care will always remain close to my heart.

I acknowledge the financial assistance from University of Groningen (**RUG**) for providing me Ubbo Emmius Fellowship and Child care support during my doctoral research. Courses and financial support from Graduate School for Drug Exploration (**GUIDE**) are also highly acknowledged. Special thanks to European Association for the Study of the Liver (**EASL**) for providing Young Investigator Bursary Fellowships to attend highly informative and stimulating EASL conferences and meetings, and I am also grateful to **EASL** for providing me Sheila Sherlock Research Fellowship to pursue my postdoctoral research at Karolinska Institute.

I want to express my gratitude for the countless **mice** for sacrificing their lives without which my doctoral research would have never been accomplished. I hope this work (and their lives) will help in the development of future treatment for the chronic diseases.

I am deeply indebted to my **family** [**Papa, Mumma, My sisters** (Rekha, Anu), **brother-in-laws** (Ajay Jijaji and Surabhji) and my little **brother** (Neeraj)] for their tender and unselfish love, blessings and support throughout my life. My deepest thank is due to my **father-in-law**, who always encouraged me during my PhD and for his blessings. I am sure he will be proud of me when I will finally receive my PhD degree. I express my sincere gratitude to my **mother-in-law, brother-in-laws** (Vishal Bhaiya and Rajesh Jijaji) and **sister-in-laws** (Chanchal Bhabhiji and Rashmi Didi) for their affection and immense care. My love is always unlimited to my little **niece** and **nephews** who were always waiting for me back in India and gave me so much love and happiness. I also convey my gratitude to all my near and dear ones, those who behind the scenes have encouraged me and supported me at different steps of my life.

Last but not the least, I want to thank my loving **husband**, without whom my venture would have been incomplete. His warm love, affection and moral support made me to pass through all the hurdles I have faced during my PhD. He always motivated me with his positive thoughts and relieved my tensions with his smile and care. Without you being in my life, I would have been incomplete and would have never stood anywhere. You gave me strength, self-confidence and showed me what I am and what I can achieve. Thanks for being at my side and for being my better half. My love and blessings always stays with my little and sweet son **Ishaan**, who was five months old when I started my PhD. He gave me so much affection and hundreds of reasons to smile that relieved my tensions and stress of work. I hope mumma didn't bother you when mumma was busy with PhD. I will wait for the day when you are big enough to read this.

*Ruchi Bansal*



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**Personal information**

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Ruchi Bansal (Maiden Name: Tayal)

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**Education and Research Experience**

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**Postdoctoral research (July 2011-present):** Karolinska University hospital Huddinge, Stockholm, Sweden

- *Project title:* The role of HCV proteins and alcohol in the pathogenesis of HCV-induced fibrogenesis.
- *EASL Sheila Sherlock research fellowship* granted by European Association for the study of the liver.

**Ph.D. (Sept. 2007-June 2011):** University of Groningen, The Netherlands

- *Thesis title:* Re-direction of Interferon gamma and its signalling moiety: new options for the therapy of chronic diseases.
- *Ubbo Emmius Fellowship from Dutch Ministry of Foreign Affairs. Project Advisors:* Prof. Klaas Poelstra (Supervisor), Dr. Jai Prakash (Co-supervisor), Dr. Leonie Beljaars (Co-supervisor).

**Senior Research fellow (2004-2007):** All India Institute of Medical Sciences, Delhi, India.

- *Project titles:* (a) Development of antigen specific non-radioactive reporter based T-cell cytotoxicity assay. (b) Generation of HBV core-Linker-Firefly Luciferase for the development of ELISA for the detection of anti-human HBV core antibody.
- *Senior Research fellowship* granted by Council for Scientific and Industrial Research (CSIR), India. *Project Advisors:* Prof. Subrat Kumar Panda (Department of Pathology) and Prof. Subrat Kumar Acharya (Department of Gastroenterology).

**Junior Research fellow (2002-2004):** All India Institute of Medical Sciences, Delhi, India.

- *Project titles:* (a) Occult hepatitis B virus infection in chronic liver disease: full-length genome and analysis of mutant surface promoter. (b) Sequence analysis of Hepatitis E virus 3' terminal sequences from blood donors, patients and animals.
- *Junior Research fellowship* granted by Council for Scientific and Industrial Research (CSIR), India. *Project Advisors:* Prof. Subrat Kumar Panda (Department of Pathology) and Prof. Subrat Kumar Acharya (Department of Gastroenterology).

**M.Sc (Honors) in Biochemistry (2000-02):** Delhi University, Delhi, India.

- *Project Advisors:* Prof. Vijay Kumar Chaudhary, Prof. Anil Kumar Tyagi and Prof. Prahlad. C. Ghosh.
- *Master thesis titles:* (a) Liposome mediated delivery of Ricin in CHO cells and Effects of Various lysosomotropic agents; (b) Expression, phage display and mapping of HIV P24 protein.

**B.Sc (Honors) in Biochemistry (1997-2000):** Sri Venkateshwara College, Delhi University, New Delhi, India.

## Awards

- *EASL Young Investigator bursary award*, European Association for the Study of the Liver (EASL) monothematic conference 2011 held in Petersburg, Germany.
- *EASL Young Investigator bursary award*, International Liver Congress, EASL 2011 held in Berlin, Germany.
- *Nominated from University of Groningen (RUG)* for Netherlands Federation of Innovative Drug Research (FIGON) National PhD competition 2010.
- *2<sup>nd</sup> Best Poster Presentation award* at FIGON Dutch Medicine Days 2010, Lunteren, The Netherlands.
- *EASL Young Investigator bursary award*, International Liver Congress, EASL 2010 held in Vienna, Austria.
- *Young Investigator travel Grant* from Department of Biotechnology (DBT), Ministry of Science and technology, India for attending 12<sup>th</sup> ISVHLD 2006, Paris, France.
- *Council of Scientific and Industrial Research (CSIR) research fellowship* from 2002 - 2007.
- *Received Indira Gandhi Memorial award for second university rank in B. Sc. (H) Biochemistry* in 2000, by Delhi University, India.
- *Received Shri Nari Mirchandani memorial prize (1995-1996) for scoring highest percentage in Biology.*
- *Received Merit cum means cash award (1994-1995) in class XI.*
- *Awarded membership of the European Association for the study of the liver (EASL), Switzerland, 2010-2012.*

## Fellowships

- *EASL Sheila Sherlock Research Fellowship* from June 2011 – May 2012 awarded for Postdoctoral research at Karolinska Institutet at Karolinska University Hospital Huddinge in Stockholm, Sweden.
- *Ubbo Emmius International fellowship* from Sept 2007 – August 2011 to pursue PhD at the University of Groningen, The Netherlands.
- *Council of Scientific and Industrial Research (CSIR) research fellowship* from August 2002 – July 2007 for research at AIIMS, Delhi, India.
- *Awarded IndusInd fellowship, IndusInd Foundation, India for the University Education (1997-2000).*

## List of publications:

### From this thesis

- **Bansal R**, Post E, Proost JH, de Jager-Krikken Alie, Poelstra K, Prakash J. PEGylation improves pharmacokinetic profile, liver uptake and efficacy of Interferon gamma in liver fibrosis. *Journal of Controlled Release* 2011; 154 (3): 233-240.
- **Bansal R**, Prakash J, Post E, Beljaars L, Schuppan D, Poelstra K. Novel engineered targeted Interferon gamma blocks hepatic fibrogenesis in mice. *Hepatology* 2011; 54 (2): 586-96.  
*"Research highlight" published in Nature Reviews Gastroenterology and Hepatology, 2011; 8 (7): 359.*  
*Highlighted as "key scientific article" in Global Medical Discovery.*
- **Bansal R**, Prakash J, de Ruiter M, Beljaars L, Poelstra K. Peptide-modified albumin carrier explored as the targeted approach to deliver interferon gamma for the treatment of liver fibrosis. *Molecular Pharmaceutics* 2011; 8 (5): 1899-1909.
- **Bansal R**, Tomar T, Ostman A, Poelstra K, Prakash J. Selective targeting of interferon gamma to stromal fibroblasts and pericytes as a novel therapeutic approach to inhibit angiogenesis and tumor growth *Molecular Cancer Therapeutics (Accepted)*.
- **Bansal R**, Prakash J, de Ruiter M, Beljaars L, Poelstra K. Targeted delivery of Interferon gamma peptidomimetic inhibits chronic hepatic fibrosis and tumor angiogenesis in vivo (*Submitted*).
- **Bansal R**, Prakash J, de Ruiter M, Poelstra K. Recombinant engineered HSC-specific targeted fusion proteins of IFN $\gamma$  and mimetic IFN $\gamma$  with PDGF $\beta$ R bicyclic peptide inhibits liver fibrosis in vivo (*Manuscript in Preparation*).

### Other publications

- Prakash J, **Bansal R**, Post E, de Jager-Krikken A, de Hooge, MH, Poelstra K. Albumin-binding and tumor vasculature determine the anti-tumor effect of 15-deoxy-delta<sup>12,14</sup>-Prostaglandin-J<sub>2</sub> in vivo. *Neoplasia*. 2009; 11(12): 1348-58.
- Gupta P, **Tayal R**, Durgapal H, Rath S, Acharya SK, Panda SK. Development of highly sensitive Bicistronic vector based non-radioactive antigen-specific cytotoxicity assay. *Journal of Immunological Methods* 2009; 349(1-2): 28-37.
- Chaudhuri V, **Tayal R**, Nayak B, Acharya SK, Panda SK. Occult hepatitis B virus infection in chronic liver disease: full-length genome and analysis of mutant surface promoter. *Gastroenterology* 2004; 127(5): 1356-71.

### Patent

**Bansal R**, Poelstra K, Prakash J, Beljaars L. Interferon-gamma analogues for the treatment of liver fibrosis. Issued on Jan 2010. European patent application (EP

09181049.9); US application (US 61/302973) and PCT application (PCT/NL2010/050897).

### **Published abstracts**

- **Bansal R**, Prakash J, Ruijter M De, Post E, Beljaars L, Poelstra K. A novel interferon gamma peptidomimetic inhibits early and progressive liver fibrogenesis in vivo. *Hepatology* (2011); 54 (suppl. 4): 732A. Selected as AASLD Presidential Poster of Distinction.
- Prakash J, **Bansal R**, Tomar T, Ostman A, Poelstra K. Targeting of Interferon gamma to stromal fibroblasts using a PDGF receptor recognizing carrier reduces tumor growth in vivo". *European Journal of Cancer* 2011; 47 (suppl. 1): S217.
- **Bansal R**, Prakash J, Ruiters M de, Post E, Beljaars L, Poelstra K. Delivery of the Interferon gamma signaling moiety to the PDGF $\beta$ -receptor on Hepatic Stellate Cells ameliorates established liver fibrosis in mice. *Journal of Hepatology* (2011); 54 (suppl. 1): S419. Selected by editorial panel as "poster of the week" and "most viewed poster of the month" by F1000 posters. *F1000 Research* 2011, 2, 1056 (poster)
- **Bansal R**, Prakash J, Post E, Beljaars L, Poelstra K. Resolution of advanced liver fibrosis by targeted delivery of interferon gamma to hepatic stellate cells using a PDGF $\beta$ R-recognizing cyclic peptide: improved therapeutic efficacy and no adverse effects. *Hepatology* (2010); 52 (suppl. 1): 1264A – 65A.
- **Bansal R**, Prakash J, Proost JH, Post E, Jager-Krikken A de, Beljaars L, Poelstra K. Anti-fibrotic effects of PEGylated interferon gamma in vitro and in vivo in acute CCl<sub>4</sub>-induced liver injury mouse model: Therapeutic efficacy and adverse effects. *Hepatology* (2010); 52 (suppl. 1): 1282A.
- **Bansal R**, Prakash J, Post E, Beljaars L, Poelstra K. Cell-Specific Targeting of Interferon Gamma to hepatic stellate cells using a cyclic PDGF-receptor recognizing peptide improves its therapeutic efficacy. *Journal of Hepatology* (2010); 52 (suppl. 1): S354-S355.
- **Tayal R**, Durgapal H, Acharya SK, Panda SK. Development of Non-radioactive antigen-specific reporter release T-cell cytotoxicity assay. *Hepatology International* 2007; 1 (suppl. 1): P920.
- **Tayal R**, Durgapal H, Satpathy G, Acharya SK, Panda SK. Development of bicistronic selectable vector for non-radioactive antigen specific reporter release T-cell cytotoxicity assay. *Journal of Clinical Virology* 2006; 36 (suppl. 2): S158.
- **Tayal R**, Thakral D, Durgapal H, Dixit R, Acharya SK, Panda SK. Sequence analysis of hepatitis E virus 3' terminal sequences from blood donors, different diseased patients and animals. *Journal of Gastroenterology and Hepatology* 2004; 19 (suppl. 7): A821.

## Oral Presentations

- Targeted interferon gamma and mimetic interferon gamma explored as potential therapeutics for the treatment of liver fibrosis. *EASL monothematic conference 2011 at Petersberg, Germany, June 17<sup>th</sup> – 18<sup>th</sup>, 2011.*
- Cell-specific delivery of Interferon gamma in the fibrotic liver; therapeutic efficiency and adverse effects. *Dutch Science Liver Retreat (DSLRL) at Westerbork, Netherlands, October 14<sup>th</sup> - 15<sup>th</sup>, 2010.*
- Liver-specific targeting of Interferon gamma to hepatic stellate cells inhibits advanced liver fibrosis in mice with potentially reduced side effects. *FIGON Dutch Medicine Days at Lunteren, Netherlands, October 4<sup>th</sup> - 6<sup>th</sup>, 2010.*
- A novel hepatic stellate cell targeted chimeric peptide of mimetic IFN $\gamma$  inhibits liver fibrosis in acute CCl<sub>4</sub>-induced liver injury mouse model. *4<sup>th</sup> European Club for Liver Cell Biology (ECLCB) meeting, Castillo de Javier, Pamplona, Spain, September 30<sup>th</sup> - 2<sup>nd</sup> October 2010.*
- Liver-specific targeting of Interferon gamma to hepatic stellate cells inhibits experimental liver fibrosis in mice with potentially reduced side effects. *GUIDE Early Summer Meeting, Groningen, Netherlands, June 10, 2010.*
- A mimetic peptide of Interferon gamma (IFN gamma) as a novel anti-fibrotic agent. *Keystone Symposia Conference, Fibrosis (J2), at Keystone, Colorado, USA, January 20<sup>th</sup> - 25<sup>th</sup>, 2009.*
- Liver-selective delivery of Interferon gamma for the treatment of liver fibrosis. *GUIDE Early Summer Meeting, Groningen, Netherlands, June 5, 2008.*

## Poster Presentations

- Targeted interferon gamma and mimetic interferon gamma explored as potential therapeutics for the treatment of liver fibrosis. *European Association for the Study of the Liver (EASL) monothematic conference 2011 at Petersberg, Germany, June 17<sup>th</sup> – 18<sup>th</sup>, 2011.*
- Delivery of the Interferon gamma signaling moiety to the PDGF $\beta$ -receptor on Hepatic Stellate Cells ameliorates established liver fibrosis in mice. *EASL International Liver Congress 2011 at Berlin, Germany, March 30<sup>th</sup> – April 3<sup>rd</sup>, 2011.*
- Resolution of advanced liver fibrosis by targeted delivery of interferon gamma to hepatic stellate cells using a PDGF $\beta$ R-recognizing cyclic peptide: improved therapeutic efficacy and no adverse effects. *American association for study for liver diseases (AASLD) Liver meeting 2010 at Boston, USA, November 2010.*
- Anti-fibrotic effects of PEGylated interferon gamma in vitro and in vivo in acute

CCl<sub>4</sub>-induced liver injury mouse model: Therapeutic efficacy and adverse effects. *American association for study for liver diseases (AASLD) Liver meeting 2010 at Boston, USA, November 2010.*

- Liver-specific targeting of Interferon gamma to hepatic stellate cells inhibits advanced liver fibrosis in mice with potentially reduced side effects. *FIGON Dutch Medicine Days at Lunteren, Netherlands, October 4<sup>th</sup> - 6<sup>th</sup>, 2010.*
- Liver-specific targeting of Interferon gamma to hepatic stellate cells inhibits experimental liver fibrosis in mice with potentially reduced side effects. *GUIDE Early Summer Meeting, Groningen, Netherlands, June 10, 2010.*
- Cell-Specific Targeting of Interferon Gamma to hepatic stellate cells using a cyclic PDGF-receptor recognizing peptide improves its therapeutic efficacy. *EASL International Liver Congress 2010 at Vienna, Austria, April 14<sup>th</sup> - 18<sup>th</sup>, 2010.*
- Intracellular delivery of Interferon gamma to human hepatic stellate cells using pegylated PDGF receptor specific carrier: A novel approach for the treatment of liver fibrosis. *GUIDE Early Summer Meeting, Groningen, Netherlands, June 4, 2009.*
- A mimetic peptide of Interferon gamma (IFN gamma) as a novel anti-fibrotic agent. *Keystone Symposia Conference, Fibrosis (J2), at Keystone, Colorado, USA, January 20<sup>th</sup> - 25<sup>th</sup>, 2009.*
- Liver-selective delivery of Interferon gamma for the treatment of liver fibrosis. *GUIDE Early Summer Meeting, Groningen, Netherlands, June 5, 2008.*